Why is Long Term Safety So Important in Pediatrics?

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Disclaimers

- The views expressed in this presentation are those of the speaker, and do not necessarily represent the policies of the Department of Health and Human Services or the Food and Drug Administration.
- There are no financial conflicts of interest to disclose.

Stating the "Obvious"

- Everyone "knows" children grow, develop and learn
- The complexity and enormity of these changes are sometimes forgotten in the "knowingness" of daily life
- Science/ Medicine are constantly changing and yesterday's "dogma" is tomorrow's "mistake" or "partial knowledge"

The most dynamic changes occur in the first 18 years of life

- Neonates are a physiologic environment unto themselves and we still have much to learn
- Childhood involves growth velocity never seen in any other period
- Bone and muscle changes are dramatic as movement goes from crawling to standing and running
- Enzymatic activation, immunologic development and physiologic changes continue to develop during childhood and adolescence
- Neurological/cognitive development is most dynamic during the first 18 years: from no speech to complex problem solving
- Puberty is a hormonal and growth “storm” of changes only part of which includes reproductive organ development

Barriers to Pediatric Product Development

- Children are a small % of the population size
  -not as big a market - fewer to enroll in studies
- Children are usually healthy
- Children have additional ethical “rules”

- More difficult to conduct pediatric trials
  - Limited patient population to study
    - Children’s illnesses tend to be acute so limited chronic patient population to study
    - Small populations → multicenter and often international studies to enroll an adequate number of patients.
    - Special facilities, equipment, nurses, laboratories and expertise are needed.

- Parents must be involved, and often the family

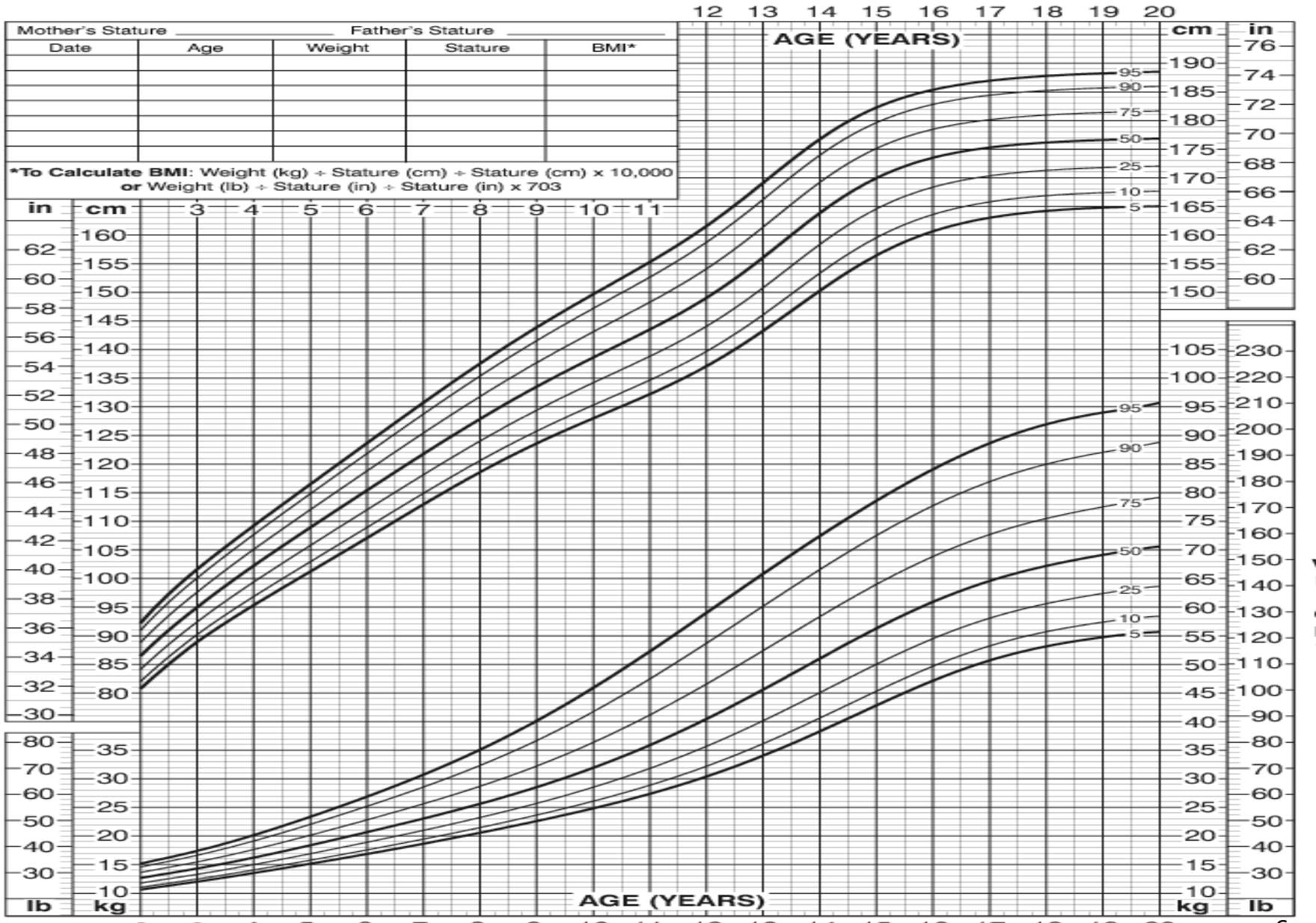
2 to 20 years: Boys
Stature-for-age and Weight-for-age percentiles

NAME _____

RECORD # _____

Mother's Stature _____		Father's Stature _____		
Date	Age	Weight	Stature	BMI*

*To Calculate BMI: Weight (kg) ÷ Stature (cm) ÷ Stature (cm) x 10,000
or Weight (lb) ÷ Stature (in) ÷ Stature (in) x 703



Published May 30, 2000 (modified 11/21/00).
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
http://www.cdc.gov/growthcharts

CDC
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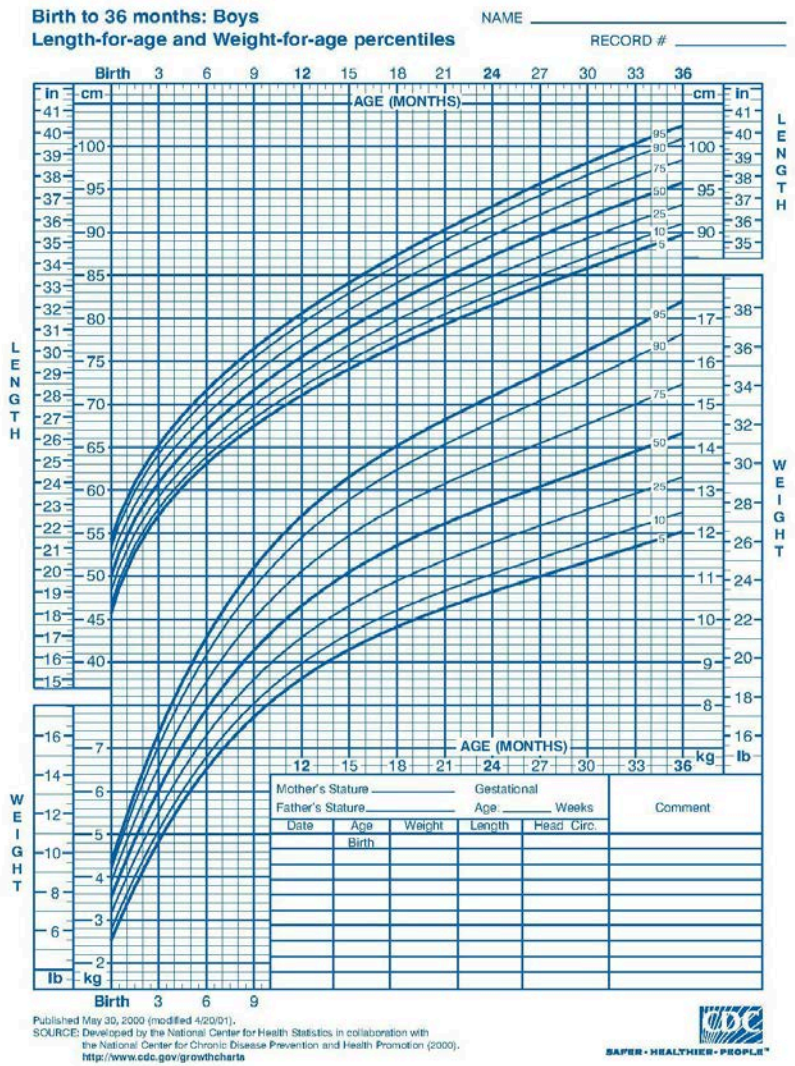
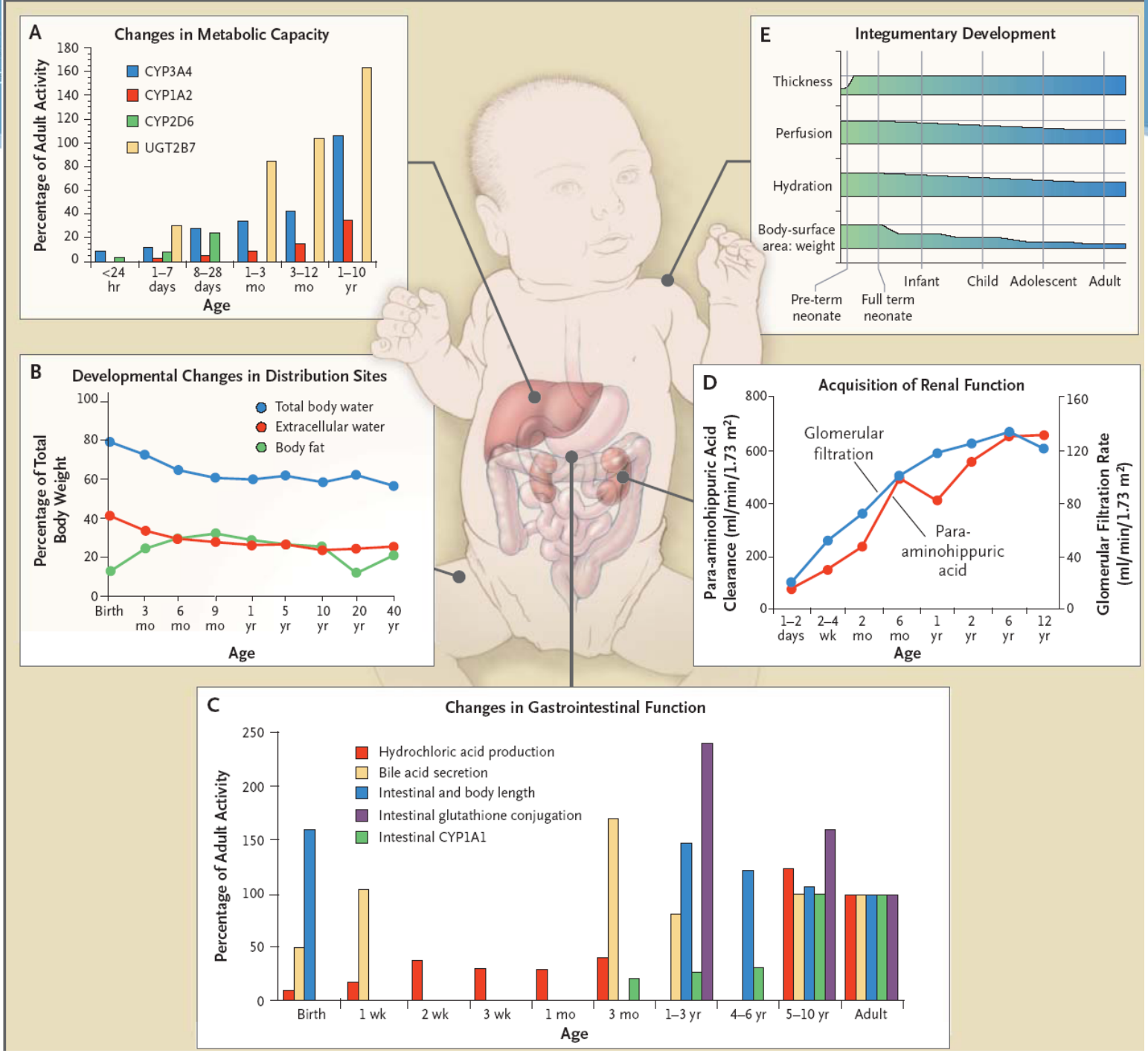
Pediatric Growth Chart: 0-36





Kearns et al.,
NEJM 349: 1160

What we forget

- How much we still do not know about the <u>developmental</u> processes at the genetic, cellular, receptor and basic science level
- How little we really still know, despite studying over 600 therapeutics

  = We did not begin routinely studying drug therapies in pediatrics until the very end of the 20th century (1997),
- That certain populations, such as neonates & children with rare diseases, remain mostly unstudied in relation to therapeutic trials meeting FDA's standards required for adult therapies
- That we have VERY LITTLE information on what a lifetime of exposure to a therapeutic may do to the developing organism's many developing systems
- Most studies are for very short periods and do not provide information on what happens to developmental systems over many years of exposure

Issues for ALL therapeutic trials

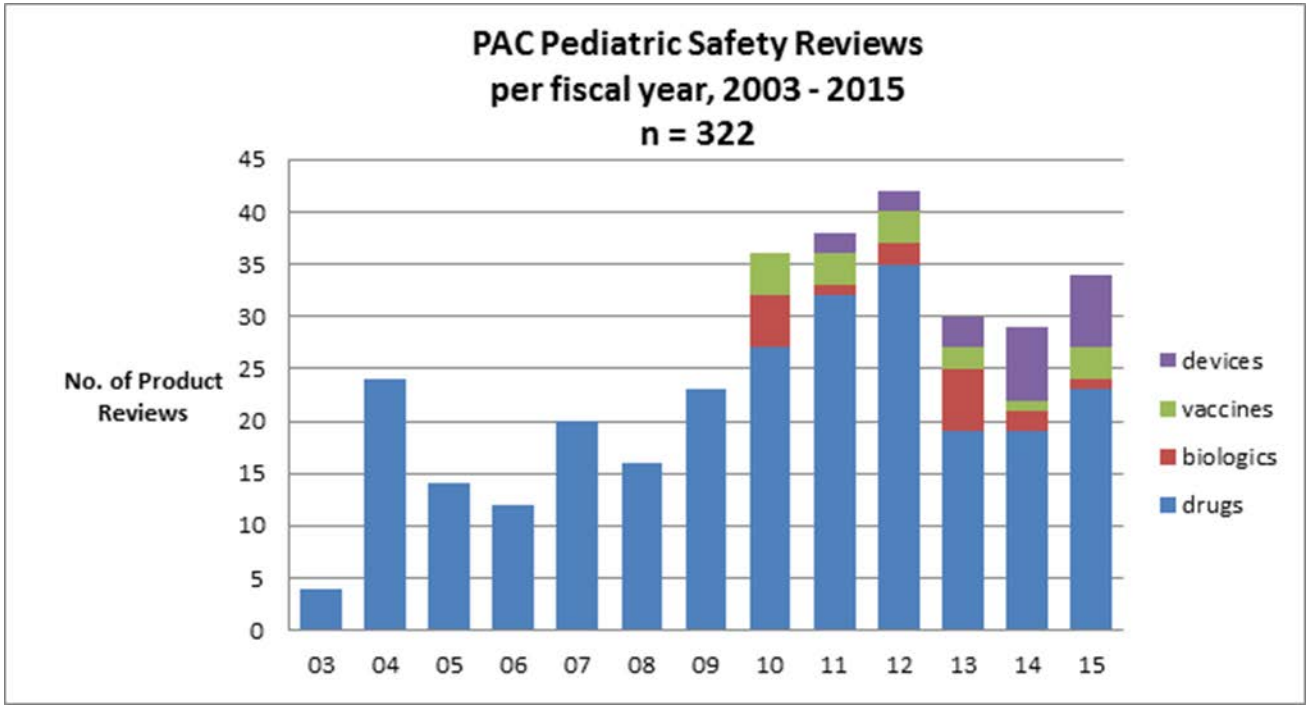
- Trials involve only a small part of the population that will use the product when determining safety and efficacy
- Clinical trials control who can enroll and thus cannot identify all the potential risks as people with other conditions or medicines will eventually take the drug
- This means that at the time of a medicine's authorisation, it will only have been tested in a relatively small number of patients for a limited length of time
- Some adverse reactions may not be seen until healthcare professionals begin prescribing to a broader group of patients
- It is therefore important to remember that we really know a limited amount about a product's safety when it is marketed

How do we know there is a potential difference in safety between adults and pediatrics?

Overview of over a decade of mandated Post-marketing Safety Reviews

- This review occurs 18 months post labeling
- 2003 to the present: N=322 products
- Products = any product studied under the pediatric legislation and labeled with new pediatric information
- Since 2007 this includes “negative studies”
- The majority of products are referred back to “routine safety monitoring”- this is good BUT
- “Routine” for pediatrics risks being “lost” in the larger sea of adverse events reported for adults for any one product that is used by both populations
- What happens when children have been on a therapy as they go thru the various developmental stages is not known

Pediatric Advisory Committee Reviews: 2003-2015



Examples of "found" pediatric safety issues during these Reviews

Pediatric Unique issues

- Androgel: cutaneous transfer to children results in virilization, premature puberty clitoromegaly and surgery for such
- Suicidality rates in adolescents
- Incipients causing adverse effects
- Continued use of a "failed" product: Failed studies in pediatrics with some products already approved as effective in adults

Examples of "found" pediatric post-marketing safety issues

- Increased expression or rates of AE's in the pediatric population
  - neurocognivite AE's with a number of products
- Excessive weight gain and increased incidence of metabolic syndrome in adolescents on antipsychotics
- Higher rate of hospitalization and exacerbation of asthma for LABA's

Issues with Data Sources

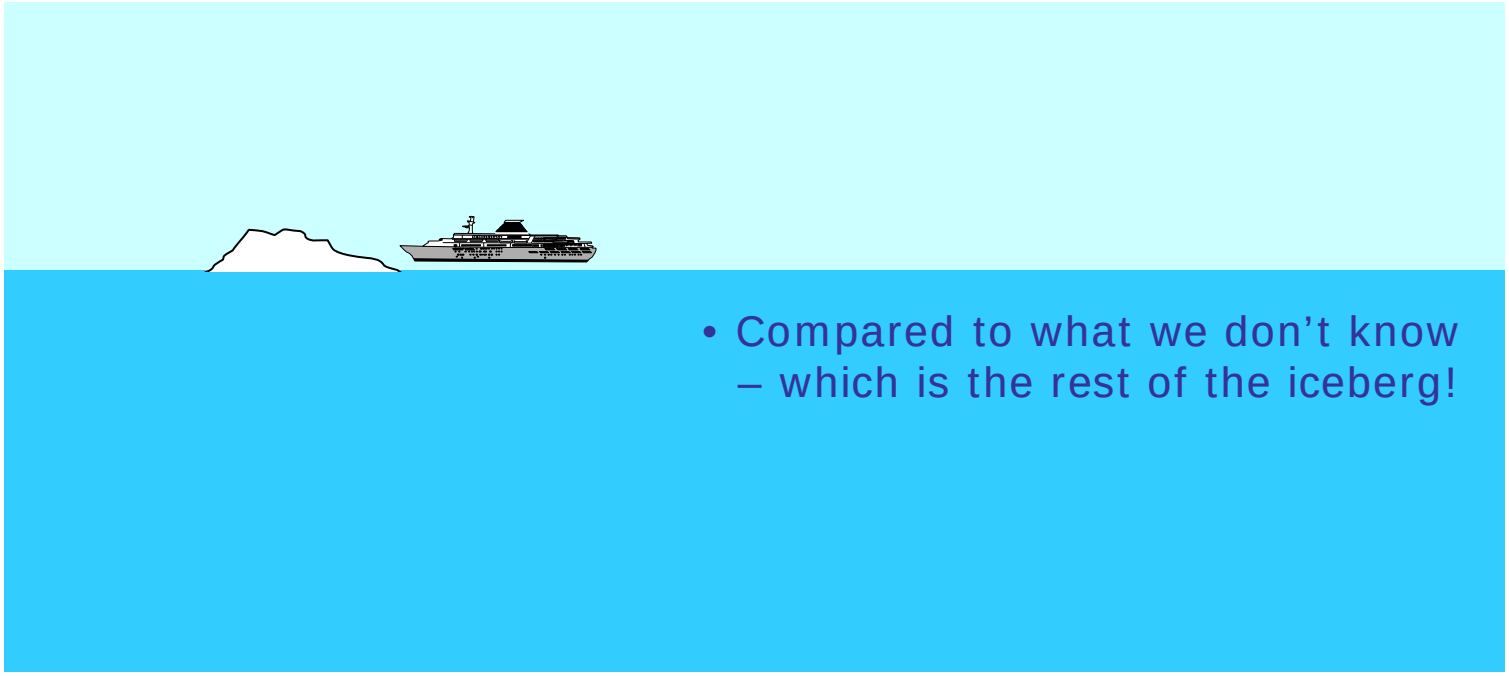
- Age maybe missing
- Pediatric specific concerns such as growth and development may not be addressed
- Laboratory values may not be pediatric appropriate
- Coding of problems specific for pediatrics into adult codes

Where are we today?

- You will hear a presentation today about the usual “duration” of pediatric studies
- None of these studies provide information on safety of a product over the many developmental changes that occur in pediatrics
- There are many reasons to NOT be requesting long term studies in children at this time
- There remain many questions on what the long term impact of therapies might be on various organ or developmental systems

Having spent vast sums of money and years developing a medicine, the view of many drug developers, healthcare professionals and patients is that the **drug is pretty well known**.

However in reality what we know at the end of the clinical trial programme is just the **tip of the iceberg**.

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NATURES OWN REMEDY

Though we are making progress, we still have a long way to go.

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Pediatrics

- New Pediatric Labeling Information Database
- Safety Reporting Updates
- Pediatric Study Characteristics Database
- List of Exclusivity Determinations (PDF - 179KB)
- Medical, Statistical, and Pharmacology Reviews 7/9/2012- present

Spotlight

- Gaucher disease - A Strategic Collaborative Approach from EMA and FDA
- Public Workshop – Pediatric Clinical Investigator Training
- 2014 Meeting Materials, Pediatric Advisory Committee to the FDA
- AAP News FDA Update
- FDA Pediatric Safety Communications

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